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CHAPTER 15

General Pharmacology of Glucocorticoids

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ANTI-INFLAMMATORY STEROID ACTION
BASIC AND CLINICAL ASPECTS
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I. Introduction

Since the introduction in 1949 of corticosteroid therapy to clinical medicine in treating rheumatoid arthritis, intense effort has been made to develop methods to maximize the beneficial effects of this potent group of medications. Investigations are directed to understand how the body synthesizes, metabolizes, and regulates the amount of these hormones available at any given time. In addition, it is important to understand mechanisms of action and apply this information in the development of synthetic compounds that increase the ratio of desired effects to those not essential for a specific therapeutic application.

The corticosteroids are hormones synthesized in and secreted from the adrenal cortex (Simpson and Mason, 1979). They may be classified in relation to pharmacologic effect as *glucocorticoids* and *mineralocorticoids*. The glucocorticoids—for example, cortisol—play a significant role in carbohydrate, protein, and fat metabolism, as well as exerting an anti-inflammatory effect. Anti-inflammatory properties refer to the characteristics of corticosteroids that prevent or suppress the development of local heat, redness, swelling, and tenderness. The mineralocorticoids, such as aldosterone, influence water and electrolyte balance. Although it is feasible to develop synthetic agents that have more potent glucocorticoid effect as compared to mineralocorticoid effects, it is not possible to separate the anti-inflammatory effects of glucocorticoids from the metabolic effects. Furthermore, the glucocorticoids significantly suppress hypothalamic–pituitary–adrenocortical (HPA) function and, therefore, sudden cessation of chronic therapy can severely alter physiologic homeostasis.

This discussion will review the general principles of glucocorticoid therapy. These relate primarily to the desired anti-inflammatory effects of corticosteroids. It must be recognized that methods to increase the anti-inflammatory effects are associated with an increased risk for undesired effects, such as growth suppression, alterations in body habitus, osteoporosis, hypertension, and cataracts—to name a few. Nevertheless, these agents are beneficial in managing many inflammatory disorders, such as asthma and collagen vascular disease, as well as neoplastic disease, shock, and inhibition of transplant rejection. Methods to optimize effect include the identification of compounds that maximize the ratio of glucocorticoid to mineralocorticoid effects, attempts to deliver the most drug to the relevant site of action, and to define dosing schemes to maintain beneficial effects while minimizing HPA axis suppression.

This discussion will review primary components influencing the response to corticosteroid therapy, including structure–activity relationship, pharmacokinetics, pharmacodynamics, and clinical applications. Also included will be a review of conditions that may contribute to inadequate response to steroid therapy.

II. Determinants of Response to Steroid Therapy

The primary application of corticosteroid therapy is directed toward the anti-inflammatory effects of these compounds. With the attendant risk for serious adverse effects, it is necessary to confirm the diagnosis before beginning a long-term course of steroid therapy. Whenever possible, it is also important to maximize the use of alternative medications: for example, bronchodilators or cromolyn for asthma or salicylates for the treatment of rheumatoid arthritis. Since corticosteroids decrease the response to infection, care should be taken to determine whether latent infections, such as mycobacterial disease, are present before treatment begins.

The most significant determinants for response to corticosteroid therapy are the structural components of the administered agent. Although certain features are essential for pharmacologic effect, additional structural modifications increase the potency and duration of effect. The potency of a corticosteroid is correlated to the binding affinity of the steroid to specific receptors (Rousseau *et al.*, 1972). These structural features will be discussed in detail in the following section.

Another important determinant of response to steroid therapy relates to the systemic disposition of the individual compounds. This is integrally related to the structure, since this will affect the rate of elimination and distribution of the steroid. Corticosteroid pharmacokinetics are also complicated by some unusual features. First is the protein-binding characteristics. Certain corticosteroids are bound to transcortin, a high-affinity, low-capacity corticosteroid-binding globulin; and albumin, a plasma protein with low affinity and high capacity. Second, certain corticosteroids, such as prednisone and cortisone, are inactive and must undergo a conversion reaction to form the active component. The implications of these observations on disposition parameters will be addressed.

The time of onset and intensity of pharmacologic effect is related to the specific corticosteroid and disposition parameters. It is likely that the cellular onset of action is immediate; but the intricate mechanisms necessary to attain the desired physiologic effect may result in a lag time for the observed beneficial effect. Prolonged exposure to corticosteroid therapy, although maintaining the desired response, may contribute to the development of adverse effects.

Information derived from past studies can be applied to develop treatment regimens to obtain the desired clinical response in individual patients. Certain factors can contribute to the development of adverse effects. This may be related to unusual impairment of steroid elimination. Other patients may respond poorly to an appropriate treatment course. Potential mechanisms for inadequate response to corticosteroid therapy will be reviewed.

III. Structure–Activity Relationship

The basic chemical structure of the glucocorticoids (Figure 1) consists of 21 carbon atoms with a total of 4 rings, three 6-carbon rings (A, B, and C), and a 5-carbon ring (D). The anti-inflammatory steroids have a 2-carbon chain at the 17 position and methyl groups at carbons 18 and 19. Other essential features of the glucocorticosteroids consist of the following: (1) a ketone oxygen at C-3; (2) an unsaturated bond between C-4 and C-5; (3) a hydroxyl group at C-11; and (4) a ketone oxygen at C-20.

Synthetic analogs are developed by substituting at sites on the cortisol molecule. The result is intended to enhance anti-inflammatory activity and reduce mineralocorticoid activity as compared to cortisol. Values for relative glucocorticoid and mineralocorticoid potency presented in Table 1 are approximations based on several sources. The introduction of an unsaturated double bond between C-1 and C-2 on cortisol provides the structure for prednisolone, which has a fourfold enhancement of corticosteroid activity as compared to cortisol.

It is commonly stated that prednisolone has mineralocorticoid activity; but there is little or no information to support this assumption. Available animal and clinical studies suggest minimal mineralocorticoid effects (Thorn *et al.*, 1955; Liddle, 1958). The biologic half-life of prednisolone is extended to 12–36 hr; for cortisol, it is 8–12 hr. Biologic half-life of glucocorticoids are characterized as short, intermediate, and long acting, based on the duration of ACTH suppression following a single dose of a corticosteroid (Harter, 1966). Cortisone and the synthetic derivative prednisone are 11-keto compounds and lack anti-inflammatory activity until converted into the 11-β-hydroxyl compounds, cortisol and prednisolone. Cortisone and cortisol, as well as prednisone and prednisolone, undergo continuous interconversion in the body, forming inactive and active

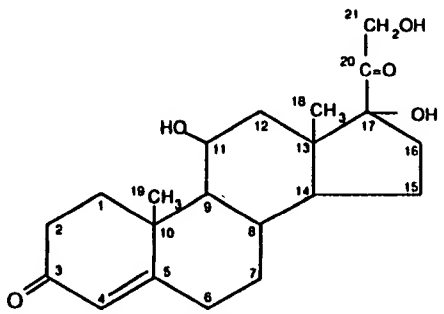

Figure 1
Structure of hydrocortisone.

Table 1
Relative Potencies of Corticosteroids

	Glucocorticoid Potency	Equivalent Glucocorticoid Dose (mg)	Mineralocorticoid Potency	Plasma $t_{1/2}$ (min)	Biologic $t_{1/2}$ (hr)
Short-acting					
Cortisol	1	25	1	90	8–12
Intermediate-acting					
Prednisolone	4	5	0	200	12–36
Methylprednisolone	5	4	0	200	12–36
Triamcinolone	5	4	0	200	12–36
Long-acting					
Betamethasone	25	0.60	0	300	36–54
Dexamethasone	30	0.75	0	300	36–54
Mineralocorticoid					
Corticosterone	0.35	—	15		
Fludrocortisone	10		125		

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compounds. The significance of this interconversion reaction in relation to systemic corticosteroid availability will be reviewed.

The addition of a methyl group at the 6α position of prednisolone forms methylprednisolone. Methylprednisolone is slightly more potent in glucocorticoid activity than prednisolone. This may seem like a minor structural modification, but there is a significant difference between methylprednisolone and prednisolone in relation to protein binding and susceptibility to inhibition or induction of metabolism. This will be discussed further in the pharmacokinetics section.

Dexamethasone is a synthetic analog with 25 times the glucocorticoid potency of cortisol and minimal mineralocorticoid effect. It is a modification of prednisolone with a fluorine atom at the 9α position (enhanced glucocorticoid activity) and a methyl group at the C-16α position (decreased mineralocorticoid activity). The biologic half-life of dexamethasone is increased to 36–54 hr. Betamethasone differs from dexamethasone only in the C-16α position, where betamethasone has a C-16β methyl group; the methyl group is at the C-16α position for dexamethasone. The anti-inflammatory potency and duration of action for the two steroids are similar.

Fludrocortisone (9α-fluorocortisol) is a minor modification of cortisol with tenfold greater anti-inflammatory activity compared to cortisol. Since it has markedly increased mineralocorticoid activity, 125 times that of cortisol, it is used primarily for this purpose.

Most steroids are poorly water soluble and may be conjugated to improve water solubility. Conjugation also affects the rate of absorption and the duration of action. The phosphate and hemisuccinate conjugates at C-21 increase water solubility of such glucocorticoids as prednisolone, hydrocortisone, and methylprednisolone, providing the feasibility for parenteral administration. Another conjugate, an acetate form of cortisone, results in slow absorption and delayed onset of action.

Further alterations at the C-17 and C-21 positions result in corticosteroids with high topical activity and minimal systemic adverse effects. Two methods can be used to develop topical steroids. A steroid can be conjugated with a poorly soluble ester group that facilitates the delivery of a relatively large corticosteroid dose with minimal systemic absorption—triamcinolone acetonide, for example. Another method is to increase the potency of a weak corticosteroid by conjugation with an ester group. An example is beclomethasone diproprionate, the 17, 21-diproprionate form of 9α-chloro, 16β-methylprednisolone. Aerosol administration results in a potent topical effect on the lung with subsequent metabolism, removal of the propionate groups, and systemic absorption of the relatively weak corticosteroid, beclomethasone (Martin *et al.*, 1975).

Present goals for corticosteroid research are to identify compounds with potent anti-inflammatory activity and minimal metabolic and mineralocorticoid effects. Furthermore, it would be useful to develop corticosteroids with site-selective pharmacologic effect to alleviate concerns for major systemic toxicity.

IV. Pharmacokinetics

The pharmacologic action of a drug depends on the dose administered and the conditions that affect the disposition of the medication, including absorption, distribution, and elimination. These conditions ultimately determine the concentration-time profile and the availability of the drug at the cellular site of action. The corticosteroids have some unique properties that significantly alter the pharmacokinetics.

A. Absorption

We have noted that corticosteroids are in general poorly water soluble. Certain structural modifications can improve water solubility for parenteral administration or to decrease water solubility to enhance topical potency for oral administration.

The most frequently used corticosteroid for oral administration is prednisone, which is itself inactive and must be converted by reduction of the ketone group at C-11 to the active form prednisolone. The conversion to prednisolone is rapid, and concentrations peak within 1–2 hr, generally reaching 5 times the concentration of prednisone (Meikle *et al.*, 1975; Rose *et al.*, 1981b; Georgitis *et al.*, 1982). The concentrations of prednisolone from oral prednisone are slightly lower than those from an oral dose of prednisolone. The difference is not sufficient to recommend the routine use of prednisolone as the oral corticosteroid in place of the commonly used prednisone.

The extent of bioavailability of prednisolone from oral prednisone is approximately 80%–90%; but certain tablet preparations of oral prednisone have been associated with inadequate absorption secondary to poor dissolution (Sugita and Niebergall, 1975). Alternatives to prednisone include prednisolone and methylprednisolone tablets for oral administration. Prednisone is most commonly used based on the cost and satisfactory bioavailability performance.

B. Interconversion

Cortisone and prednisone are converted to the active forms cortisol and prednisolone by reduction of the ketone group at C-11. The reaction between cortisone and cortisol, and also between prednisone and prednisolone, is reversible and, thus, there is a continuous interconversion reaction. Recent investigations indicate that the enzyme responsible for the interconversion reaction, 11-β-hydroxysteroid dehydrogenase (EC 1.1.1.146), comprises two enzymes (Abramovitz *et al.*, 1982). Methylprednisolone, which is administered orally as the active form, also undergoes conversion in man and the rabbit to methylprednisone (Szefler *et al.*, 1980; Ebling *et al.*, 1985).

From studies based on human fetal lung tissue, there appear to be ontogenic changes in the development of this enzyme system (Murphy, 1981). Early in

gestational age, there is a predominance of conversion from cortisol to cortisone. With increasing age, the net conversion is from cortisone to cortisol. The rate of conversion of cortisone to cortisol appears to be oxygen-dependent. In the presence of hypoxemia ($p0_2$ 30 mm Hg), the rate of conversion of cortisone to cortisol in fibroblasts *in utero* is minimal and increases significantly when the $p0_2$ is increased to 140 mm Hg (Tanswell and Smith, 1980).

The interconversion reaction takes place primarily in the liver, but has also been demonstrated in the kidney (Rocci *et al.*, 1981). The 11-β-hydroxysteroid dehydrogenase enzyme is present in the liver, kidney, lung, muscle, and placental tissue (Ganis *et al.*, 1956; Ghraf *et al.*, 1975; Lugg and Nicholas, 1978; Kolanowski *et al.*, 1981; Rocci *et al.*, 1981). The rate of conversion of cortisone to cortisol and prednisone to prednisolone can be slower in patients with liver disease (Jenkins and Sampson, 1967; Powell and Axelsen, 1972). The slower conversion in these patients, combined with impaired elimination, results in comparable bioavailability of cortisone and prednisone to that of normal volunteers. Although it is conceivable that genetic abnormalities could be present in either of the two components of 11-β-hydroxysteroid dehydrogenase and, thereby, alter the conversion reaction, clinically significant deficiencies in man have not been identified.

C. Distribution

Only limited information is available on the tissue distribution of corticosteroids. It is assumed that the free or unbound fraction of plasma corticosteroid is available for passive distribution into the cell and subsequent pharmacologic activity. This may not be true for all cell types, since in certain systems glucocorticoids may accumulate against a concentration gradient. This may result from binding by intracellular glucocorticoid receptors that may represent low-affinity intracellular or membrane binding sites or a facilitated steroid-transport system (Ballard, 1979; Rao 1981).

Traditional pharmacokinetic analysis may be influenced by the unusual protein-binding characteristics of corticosteroids, as well as the interconversion phenomenon previously described. Additional information has been obtained recently using the rabbit as an animal model for evaluating the pharmacokinetics in man. The rabbit has similar protein-binding characteristics for cortisol and prednisolone, metabolic interconversion of prednisolone-prednisone, and similar pharmacokinetic parameters—such as clearance and volume of distribution—that approximate those derived in man (Rocci and Jusko, 1981). Similar to man, metabolism also predominates as the major elimination pathway. First, pertinent aspects of corticosteroid protein binding will be reviewed. This will be followed by a discussion of tissue distribution primarily based on information derived in the rabbit.

1. Protein Binding

Cortisol and the synthetic analog prednisolone are highly protein bound, primarily to two plasma proteins. This phenomenon results from the binding of cortisol and prednisolone to transcortin and albumin. Transcortin is characterized as a high-affinity, low-capacity corticosteroid-binding globulin. As a result of the low-capacity binding characteristics, the percentage of corticosteroid bound to this plasma protein changes with increasing plasma corticosteroid concentration. Albumin is a low-affinity, high-capacity binding protein for corticosteroids. The combined influence of transcortin and albumin results in a concentration-dependent variation in total percentage protein bound (Rocci *et al.*, 1982b). At low plasma cortisol and prednisolone concentrations, approximately 90% plasma corticosteroid is bound to transcortin and albumin. At higher corticosteroid concentrations, transcortin-binding sites become saturated, resulting in a larger fraction of free cortisol and prednisolone.

The elimination of cortisol and prednisolone depends on drug metabolism, and the rate of elimination is related to the free fraction of drug available to the cell. As a result of the concentration-dependent binding, the clearance of cortisol and prednisolone increases with the dose administered as determined by traditional pharmacokinetic analysis of total plasma steroid concentration (Rose *et al.*, 1981b).

Methylprednisolone and dexamethasone are minimally bound to transcortin and essentially bound only to albumin. The percentage bound to plasma proteins for these two corticosteroids is, therefore, essentially constant. Since the protein binding is concentration independent, methylprednisolone clearance remains constant regardless of dose (Szefler *et al.*, 1986).

2. Tissue Distribution

With the unusual protein-binding characteristics and the interconversion reaction, it is difficult to assess tissue distribution for the corticosteroids. Fortunately, the rabbit is a useful animal model to evaluate the influence of the interconversion phenomenon on traditional pharmacokinetic analysis of distribution volumes. Two techniques can be used to derive information related to specific tissue uptake and total distribution.

To evaluate specific tissue uptake, Khalafallah and Jusko (1984) utilized a continuous infusion technique with prednisolone to minimize the influence of concentration-dependent protein binding. Prednisolone was infused to steady state to attain plasma concentrations between 362–4528 ng/ml, comparable to those obtained during treatment with prednisone and prednisolone. Blood components and various tissues were analyzed for prednisolone and prednisone. Tissue binding was compared to the unbound prednisolone measured in plasma by equilibrium dialysis.

Tissue binding was calculated from the ratio of tissue to unbound plasma

concentrations (*Kp*). The small intestine (*Kp* = 6.65), heart (2.92), kidney (2.91), lung (2.86), skeletal muscle (1.54), and spleen (1.16) exhibited linear *Kp* values and percentage of tissue binding. Liver uptake was nonlinear, with apparent tissue binding increasing at a slower rate than the increase in plasma concentration. The tissue-to-free-plasma prednisolone ratio in the liver ranged from 4.47–0.38 *Kp* from the lowest to highest plasma concentrations. An apparent plateau was observed in the concentration of prednisolone in the liver.

The steroid binding in tissue with *Kp* greater than 1 indicates that the tissue steroid concentration exceeds the free plasma concentration, and there is binding to cellular components. Prednisolone appeared to distribute variably among the tissue. Several tissues exhibited relatively little drug uptake—for example fat tissue, brain, and cerebrospinal fluid. In total steroid uptake, skeletal muscle accounted for retaining 60% of the steady-state body load of prednisolone.

Another technique utilized to analyze tissue distribution in the rabbit model is the infusion of single doses of radiolabeled methylprednisolone and methylprednisone (Ebling *et al.*, 1985). Infusion of these compounds and subsequent analysis of concentration-time profiles permit analysis of the rate of formation of methylprednisolone from methylprednisone and the reverse process. Elimination parameters for each steroid can be calculated, as well as distribution parameters. These studies indicate that traditional pharmacokinetic analysis tends to underestimate true metabolic clearance by approximately 30%. The steady-state volumes of distribution are overestimated by 10% for methylprednisolone and 61% for methylprednisone. This is largely related to the interconversion phenomenon. Because of the continual recycling of corticosteroid in this reaction, the systemic availability of a given dose of methylprednisolone approximates 150%, unlike the system where back conversion to methylprednisone is assumed to be absent (W.J. Jusko, personal communication). In this situation, methylprednisone is similar to a minor storage pool for the steroid.

Questions relating to the clinical significance of tissue distribution were recently raised by observations regarding prednisone and methylprednisolone disposition in the lung. Braude and Rebuck (1983) suggested that methylprednisolone is better able to penetrate lung acini than prednisone. These observations were made following collection of a single blood sample and bronchoalveolar lavage (BAL) fluid after administering a steroid dose before the procedure. Although the ratio of BAL to serum concentration was 0.5 for methylprednisolone (normalized for serum and BAL fluid creatinine; the ratio was 0.3 for prednisolone), there are several aspects of the study that may affect the application of this information.

The study design for the two steroids differed. Methylprednisolone was administered intravenously at a dose of 125–500 mg 1 hour before the procedure. Prednisone was administered orally at a lower dose, 10–60 mg, 3 hours before the procedure. Total corticosteroid concentration was measured and, therefore, the unbound fraction that influences distribution was not considered in the data analysis. Furthermore, the low prednisolone concentrations measured in BAL fluid are lower than the usual sensitivity of the assay. Accounting for these factors may reduce the magnitude of the observed difference. Further studies are needed to compare tissue distribution of available corticosteroids and, more important, to evaluate the clinical significance of these differences.

D. Elimination

The primary route of elimination for corticosteroids consists of biotransformation, with only small amounts of parent compound eliminated through the kidney (Peterson *et al.*, 1955). Cortisol and the active synthetic glucocorticoids have a double bond in the C-4,5 position and a ketone group at C-3. Reduction of the double bond in cortisol occurs at both hepatic and extrahepatic sites, and this metabolite is inactive. Subsequent reduction of the 3-ketone group demonstrated to occur only in the liver, forms tetrahydrocortisol. The reduced A-ring metabolites are conjugated primarily in the liver and to a small extent in the kidney to water-soluable sulfate esters of glucuronides and then excreted in the kidney.

Another metabolic pathway is the continuous interconversion of cortisol–cortisone by 11-β-hydroxysteroid dehydrogenase, which occurs in a variety of tissues. Cortisol also undergoes reduction at the 20-ketone position and oxidation at C-17. Following induction with phenobarbital or phenytoin, cortisol may be metabolized through a cytochrome P450 pathway to produce 6-β-hydroxycortisol (Conney *et al.*, 1965).

Introduction of a double bond at C-1,2 results in slower metabolism caused by stabilization of the A-ring. The major metabolic enzymes involved in the transformation of prednisolone and methylprednisolone include 11-β-hydroxysteroid dehydrogenase and 20-keto-steroid reductase (Vermeulen 1959). Based on urinary steroid analysis, it appears that the metabolic fate of methylprednisolone differs from that of hydrocortisone and prednisolone (Liddle, 1958; Slaunwhite and Sandberg, 1961). The interaction of methylprednisolone and prednisolone with macrolide antibiotics and anticonvulsants provides interesting insight into the possible difference in metabolic pathways for the two steroids. This will be discussed in the section on drug interactions. Additional extrahepatic sites of corticosteroid biotransformation may be related to metabolism by gastrointestinal bacterial flora (Martin *et al.*, 1975).

The disposition of corticosteroids may be influenced by several conditions. There are indications of temporal variations in prednisolone disposition, with higher concentrations obtained following early-morning doses as compared to evening doses (English *et al.*, 1983; Meffin *et al.*, 1984). This variation in disposition, observed primarily with lower doses of prednisolone, may be a combined effect of slower prednisolone elimination in the morning and decreased absorption in the evening (Meffin *et al.*, 1984). The decreased elimination may be related to competitive inhibition by endogenous cortisol.

Since methylprednisolone and prednisolone differ in their binding characteristics, it is essential to analyze the elimination of transcortin-free prednisolone

(Szefler *et al.*, 1986). There is some indication that methylprednisolone elimination is slower, mean residence time longer, and volume of distribution greater for methylprednisolone compared to prednisolone. This type of analysis may be consistent with the observations of Braude and Rebuck (1983) suggesting better distribution of methylprednisolone in the lung.

It has also been recognized that certain disease states may significantly alter corticosteroid disposition. Severe liver disease, as well as hypothyroid disorders, may impair corticosteroid elimination, and hyperthyroidism and renal disorders may be associated with accelerated steroid elimination (Powell and Axelsen, 1972; Rocci *et al.*, 1982a). Disorders with decreased albumin are associated with accelerated corticosteroid elimination (Lewis *et al.*, 1971). There is no indication that disposition is altered in inflammatory bowel disease or asthma (Rose *et al.*, 1981a; Milsap *et al.*, 1983).

E. Drug Interactions

Medications that induce or inhibit the microsomal enzyme system alter corticosteroid elimination (Table 2). Concomitant administration of phenobarbital, phenytoin, carbamazepine, ephedrine, and rifampin are associated with enhanced corticosteroid elimination (Brooks *et al.*, 1972; Edwards *et al.*, 1974; Stjernholm and Katz, 1975; Brooks *et al.*, 1977; Bartoszek *et al.*, 1987). It appears that these apparent inducers have a greater effect on methylprednisolone elimination than on prednisolone elimination. For example, methylprednisolone elimination is increased fivefold in the presence of phenobarbital or carbamazepine therapy, but prednisolone elimination is only increased twofold (Szefler *et al.*, 1982b; Bartoszek *et al.*, 1987).

Macrolide antibiotics—specifically, troleandomycin (TAO) and erythromycin—are associated with impaired methylprednisolone elimination (Figure 2) (Szefler *et al.*, 1980; LaForce *et al.*, 1983). The interaction appears to be steroid specific since, there is no apparent effect on prednisolone elimination (Szefler *et al.*, 1982b). The disposition of methylprednisolone in the presence of TAO differs significantly from that observed in the absence of TAO (Szefler *et al.*, 1980). In the absence of TAO, methylprednisolone concentration declines in a simple first-order, multiexponential manner. Elimination of methylprednisolone elimination is unusual in the presence of TAO. The pattern is nonlinear, suggesting that elimination is perturbed by distributive effects or it changes with time. This significant inhibition of methylprednisolone disposition in the presence of TAO results in plasma concentrations significantly greater than those observed at comparable times in the absence of TAO.

The macrolide antibiotics, at full therapeutic doses, reduce the elimination of methylprednisolone by 60%; but the magnitude of effect of TAO on the inhibition of methylprednisolone elimination is related to the dose and time of administration (Szefler *et al.*, 1982a). The macrolide antibiotics form a metabolite capable of binding to cytochrome P450 to produce a hypoactive cytochrome

Table 2
Corticosteroid Interactions with Other Medications

Corticosteroid	Drug	Effect	Mechanism	Reference
Cortisol	β-adrenergic agonist	Enhanced β-agonist response	Alteration of β-receptor affinity	Ellul-Micallef and Fenech (1975b); Stephan *et al.* (1980); Fraser and Venter (1980); Davies and Lefkowitz (1983)
	Phenobarbital	Increased elimination	Increased cytochrome P-450 activity	Conney *et al.* (1965); Choi *et al.* (1971)
	Phenytoin			
	Rifampin	Decreased steroid effect	Increased elimination	Edwards *et al.* (1974); Kyriazopoulou *et al.* (1984)
Prednisolone	Antacids	Decreased steroid bioavailability	Possible physical adsorption to antacid	Uribe *et al.* (1981)
	Cimetidine	No effect		Morrison *et al.* (1980); Peden *et al.* (1984); Sirgo *et al.* (1985)
	Ranitidine			
	Oral contraceptives	Increased steroid availability	Impaired elimination, increased protein binding	Boekenoogen *et al.* (1983)
	Phenobarbital	Decreased steroid effect	Increased cytochrome P-450 activity	Brooks *et al.* (1972); Bartoszek *et al.* (1987)
	Phenytoin			
	Carbamazepine			
	Rifampin	Decreased steroid effect	Increased steroid elimination	Buffington *et al.* (1976); Hendrickse *et al.* (1979)
	Troleandomycin	No effect		Spector *et al.* (1975); Szefler *et al.* (1982b)

(continues)

Table 2 *(Continued)*

Corticosteroid	Drug	Effect	Mechanism	Reference
Methylprednisolone	Cimetidine	No effect		Green *et al.* (1984)
	Diazepam	No effect		Sjoerdsma and Kaiz (1975)
	Erythromycin	Impaired MPn elimination		LaForce *et al.* (1983)
	Phenobarbital	Probable diminished	Increased cytochrome	Sjoerdsma and Kaiz
	Phenytoin	steroid effect	P-450 activity	(1975); Baroszek *et al.* (1987)
	Carbamazepine			
	Rifampin	Decreased steroid effect	Probable increased P-450 activity	Buffington *et al.* (1976)
	Troleandomycin	Enhanced steroid effect	Partially related to impaired Mpn elimination	Spector *et al.* (1975); Szefler *et al.* (1980, 1982a); Zeiger *et al.* (1980); Eiches *et al.* (1985)
Dexamethasone	Cimetidine	No effect		Peden *et al.* (1984)
	Ephedrine	Enhanced elimination	Possible increased metabolism	Brooks *et al.* (1977)
	Phenobarbital	Increased dexamethasone elimination	Increased cytochrome P-450 activity	Brooks *et al.* (1972); Haque *et al.* (1972)
	Phenytoin			
	Theophylline	No effect		Brooks *et al.* (1977)

Figure 2

Plasma concentrations of methylprednisolone and the conversion metabolite methylprednisone vs. time following an intravenous dose of 40 mg methylprednisolone sodium succinate before and during administration of TAO. Solid line, baseline study: (●), methylprednisolone; (○), methylprednisone. Dashed line, 1 week on TAO: (▲), methylprednisolone; (△), methylprednisone. Data obtained from an 11-year-old asthmatic patient. Reprinted with permission from Szefler *et al.* (1980).

complex (Pessayre *et al.*, 1981; Delaforge *et al.*, 1983). Troleandomycin can also reduce methylprednisolone elimination in the presence of potent enzyme-inducing agents such as phenobarbital and phenytoin (Szefler *et al.*, 1982b).

Another medication associated with impaired corticosteroid elimination is oral contraceptive treatment (Boekenoogen *et al.*, 1983). There is a twofold effect observed in this situation, since increased protein binding, as well as impaired elimination, are observed. The increase in protein binding is related to the effect of estrogens on increasing corticosteroid-binding globulin levels.

Cimetidine, a medication usually associated with impaired drug metabolism, does not affect corticosteroid pharmacokinetics (Morrison *et al.*, 1980; Green *et al.*, 1984; Peden *et al.*, 1984; Sirgo *et al.*, 1985).

V. Pharmacodynamics

The effects of corticosteroids are related to transport of the steroid to the cellular site of action. The onset of effect may be immediate within individual cells but

the observed physiologic effect may take several hours. Other factors that influence response include the dose and duration of corticosteroid administration, as well as other medications that may have additive effects, either by influencing steroid disposition, interacting at the corticosteroid receptor, or influencing similar physiologic action.

A. Cellular Response

It appears that corticosteroids enter the cell by passive diffusion, although active transport mechanisms have been proposed. Cellular uptake may vary in different tissues. Tissue concentration exceeds plasma concentration in lung, heart, skeletal muscle, kidney, and small intestine. This suggests the presence of a cellular binding protein. The complex mechanisms of action have been discussed in detail in previous chapters.

B. Onset of Effect

The time of onset for physiologic response to corticosteroids varies for different sites of action. Rapid response is observed in relation to calcium-ion flux by a direct effect on calcium channels or by receptor–glucocorticoid complexes acting on processes involving dephosphorylation of intracellular proteins. The release of lipomodulin in a dephosphorylated form in neutrophils is also considered a rapid onset of action. In addition, the inhibition of adrenocorticotropic hormone and suppression of circulating eosinophils occurs rapidly.

The bronchodilator effect of corticosteroids is slower in onset of action. Significant differences in pulmonary function following prednisolone administration, unlike the placebo, occur 3 hr after administration with maximum effects observed 6–12 hr postdose (Ellul-Micallef *et al.*, 1974; Ellul-Micallef and Fenech, 1975a; Ellul-Micallef, 1982). Similarly, mechanisms that incorporate the synthesis of cellular receptors, such as the β-adrenergic receptor, may take 12 hours or longer for maximum effect (Fraser and Venter, 1980).

C. Dose-Response Relationship

There is very little known regarding the dose–response relationship of corticosteroids in the treatment of clinical disorders, such as asthma, collagen vascular disease, and inhibition of transplant rejection, to name a few. Treatment is therefore empirical, with the major goal to provide effective treatment at the lowest possible dose to minimize the risk of adverse effects.

It appears from available data that adverse effects related to corticosteroids may be immediate; for example, central nervous system, HPA suppression, electrolyte regulation, and hyperglycemic; delayed in development, such as an alteration in body fat distribution, and osteoporosis; or cumulative in effect as in cataract development. These will be discussed in detail in the section on adverse effects.

D. Drug Interactions

Coadministration of certain medications with corticosteroids can enhance or inhibit the effect of corticosteroid therapy. This may be related to similar or opposing pharmacologic effects, interaction at the receptor sites, or alteration of corticosteroid disposition. As an example, corticosteroids apparently enhance the bronchodilator effect of β-adrenergic agonists in the treatment of asthma (Ellul-Micallef and Fenech, 1975b; Stephan *et al.*, 1980). This is related to the effect of corticosteroids in enhancing the efficiency of β-agonist binding to the β-adrenergic receptor (Fraser and Venter, 1980; Davies and Lefkowitz, 1983).

We previously described how macrolide antibiotics, such as TAO and erythromycin, significantly inhibited the elimination of methylprednisolone; but, there is no apparent effect on prednisolone elimination. This interaction may partially explain the beneficial effects of combined TAO-methylprednisolone therapy in the treatment of severe steroid-requiring asthmatic patients (Itkin and Menzel, 1970; Spector *et al.*, 1975; Zeiger *et al.*, 1980; Eitches *et al.*, 1985). This combination facilitates the reduction of the maintenance steroid dose and, hence, referred to as a "steroid-sparing" effect. Whether TAO has an independent mechanism of action is the subject of future studies. The mechanism does not include a significant effect on bacterial flora, synthesis of adrenal cortical steroids, or increasing the affinity of the glucocorticoid receptor (Itkin and Menzel, 1970; Spector *et al.*, 1975; Selenke *et al.*, 1980; Engler *et al.*, 1985).

The addition of anticonvulsant therapy—specifically phenobartibal—to the treatment regimen of an asthmatic patient receiving prednisone results in deterioration of symptom control (Brooks *et al.*, 1972). Although prednisolone elimination was not specifically evaluated in this clinical study, further investigation indicates that certain anticonvulsants, such as phenytoin, carbamazepine, and phenobarbital enhance prednisolone and methylprednisolone elimination (Bartoszek *et al.*, 1987). Therefore, the basis for deterioration in clinical status is likely related to decreased systemic availability of corticosteroids in the presence of anticonvulsant therapy.

Another example of this phenomenon is the precipitation of Addisonian crisis in patients with Addison's disease who receive rifampin therapy (Kyriazopoulou *et al.*, 1984). Rifampin, similar to the anticonvulsants, accelerates corticosteroid elimination (Edwards *et al.*, 1974). This phenomenon may also explain the progressive deterioration in renal function following renal transplantation or the apparent steroid "resistance" in patients with the nephrotic syndrome when rifampin is added to a course of corticosteroid therapy (Buffington *et al.*, 1976; Hendrickse *et al.*, 1979).

VI. Clinical Applications

Corticosteroid therapy may consist of replacement, for example, in the adrenal insufficiency syndromes, therapeutic in the treatment of inflammatory disorders,

or suprapharmacologic for the prevention of transplant rejection or management of shock. In each case, the steroid dose must be appropriately initiated and properly titrated to maximize beneficial effects and minimize undesirable effects.

A. Route of Administration

A number of corticosteroid formulations are available and may be selected based on the specific application. Parenteral forms, such as hydrocortisone and methylprednisolone sodium succinate are prodrugs and must be converted to the parent compound. This conversion is very rapid and assures rapid attainment of systemic availability (Ebling *et al.*, 1984). Other parenteral forms, such as cortisone acetate and methylprednisolone acetate suspension, are designed for prolonged absorption to sustain the availability of corticosteroid concentrations. These preparations are useful in treating adrenocortical insufficiency disorders and intra-articular injections.

Oral preparations are the most commonly used form of corticosteroid therapy. It is important to select preparations that have demonstrated excellent bioavailability (Sugita and Niebergall, 1975). The most significant development in corticosteroid therapy is the introduction of topical preparations. These are designed to provide maximal concentrations of potent corticosteroid at the site of action; for example, dermatologic preparations for skin disorders and aerosol formulations for the treatment of asthma.

B. Patient Variables Influencing Response

Besides the previously described determinants of response to corticosteroid therapy, other conditions must be considered. Of obvious importance is the patient's compliance for the prescribed regimen (Patterson *et al.*, 1986). With the severity of adverse effects related to prolonged high-dose systemic corticosteroid therapy, especially those affecting physical appearance, the clinician must carefully assess the patient's attitude toward self-care. Attempts should be made to minimize steroid exposure by using alternative forms of treatment and topical corticosteroid preparations, if feasible.

Initial treatment of severe life-threatening illness requires high-dose corticosteroid therapy. The dose and duration of treatment is related to the specific disease, severity, and prognosis. High-dose steroid therapy for short periods of time, less than two weeks, has a minimal risk of adverse effects, and the steroid dose can be discontinued abruptly. More prolonged therapy requires a careful dosage reduction to avoid complications of adrenal insufficiency secondary to HPA suppression. For chronic corticosteroid therapy, attempts should be made to convert the patient to an alternate-day regimen. All doses should be administered in the morning to minimize HPA suppression. Treatment strategies will be discussed in the chapters on selected clinical disorders.

C. Apparent Steroid Resistance

Most patients respond promptly to a carefully structured course of corticosteroid therapy; certain patients, however, appear refractory. Following a careful review of the treatment regimens, as well as the patient's compliance, several factors may be considered in determining the possible refractoriness to steroid therapy.

The severity of the disease may require more aggressive treatment regimens. In addition, the presence of other clinical disorders, such as renal disese or hyper-thyroidism or concomitant medications—specifically, anticonvulsants or rifampin—may be associated with increased corticosteroid elimination. In general, the variability in elimination in a patient population without obvious conditions altering steroid elimination is approximately 25% (Rose *et al.*, 1981a). The availability of techniques to readily assess steroid disposition in patients may assist in the identification of patients with unusually rapid elimination (Ball *et al.*, 1988).

Another factor to consider is the possibility of an abnormality at the level of the corticosteroid receptor. Chrousos and colleagues (1982) described a familial disorder of apparent cortisol resistance consisting of high 24-hr mean plasma cortisol levels with the absence of stigmata of Cushing's syndrome. Plasma ACTH levels were high, and the patients were resistant to adrenal suppression by dexamethasone. The glucocorticoid receptor, as measured in peripheral leukocytes and fibroblasts, had decreased binding affinity for dexamethasone. A reduced number of cytosolic glucocorticoid receptors was also observed. The implication of this phenomenon for response to corticosteroid therapy was not identified.

In addition, Carmichael *et al.* (1981) identified a population of patients with chronic asthma with apparent corticosteroid resistance. These patients demonstrated poor response to corticosteroid therapy as determined by pulmonary function tests following a course of daily high-dose corticosteroid therapy for 7 days. These patients more frequently had a family history of asthma and a longer duration of symptoms as compared to the corticosteroid-responsive patients. The resistant patients had a relatively lower peak-expiratory flow rate in the morning compared to that measured later in the day, as well as a greater degree of bronchial reactivity to methacholine. These investigators subsequently demonstrated a defect in the expression and mobilization of complement receptors on the monocyte cell membrane (Kay *et al.*, 1981) and cellular response to corticosteroid (Poznansky *et al.*, 1984).

Grant *et al.* (1984) suggested that patients who are "steroid resistant" should not receive corticosteroid therapy. This phenomenon requires further investigation since it is not clear whether these patients would respond to more aggressive courses of corticosteroid therapy, including a trial of macrolide antibiotic therapy. It is also not apparent whether steroid refractoriness identified in circulatory cells is caused by a selective process or a systemic effect (Lampl *et al.*, 1985). In addition, the nature of the deficiency in response was not identi-

fied—for example, decreased number or binding affinity of the corticosteroid receptor.

VII. Prospectus

Although recent advances have contributed to the safe and effective use of corticosteroids in severe life-threatening disorders, chronic corticosteroid therapy is associated with significant risk for adverse effects. The development of topical formulations has reduced the systemic availability of corticosteroids while providing equivalent therapeutic response. An area of intensive investigation is the development of site-specific corticosteroid derivatives. Identification of a corticosteroid-derivative selective for cells involved in the pathogenesis of inflammatory disorders, such as asthma, could provide beneficial effects while minimizing adverse effects secondary to systemic exposure.

Until such advances are made, it is necessary to continue to identify conditions that may alter response to corticosteroid therapy. Similar to the observations of accelerated or impaired corticosteroid elimination in the presence of concomitant anticonvulsant or macrolide antibiotic therapy, it is important to evaluate the effect of other medications on the disposition of corticosteroids. Significant advances in identifying conditions influencing medications such as theophylline, anticonvulsants, and anticoagulants was facilitated by the application of methods to measure plasma concentrations of the medications. Sensitive and specific methods are available to measure corticosteroid concentrations, although they are labor intensive and require the assessment of a series of concentrations to analyze disposition. Our own laboratory has applied this technique to evaluate specific patients, and the results have been beneficial (Ball *et al.*, 1988).

Monitoring of corticosteroid concentrations can be useful in evaluating compliance, as well as the adequacy of absorption, conversion of prednisone to prednisolone, and rate of elimination. Additional insight could be provided by developing techniques to measure corticosteroid response, especially if this could be used to individualize dosage regimens.

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CHAPTER 16

Side Effects of Glucocorticoid Therapy

Lloyd Axelrod

ANTI-INFLAMMATORY STEROID ACTION
BASIC AND CLINICAL ASPECTS
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